Bipolar disorder after mefloquine treatment

We report the case of a bipolar disorder presumably induced by mefloquine.

A 50-year-old man was on holidays in the Far East. After his second dose of mefloquine (250 mg), depressive symptoms developed that made him interrupt his trip. Two weeks later, he was detained in a psychiatric hospital with worsening depressive symptoms, suicidal ideation and delusions of guiltiness and economic ruin. He was certain that the chartered accountant agency he managed was failing. He thought that he was responsible for the bankruptcy of all his customers and therefore believed that he did not deserve to eat or drink any more. He had no hallucinations and was not confused. Findings on clinical examination and results of ancillary tests were normal, CT scanning was not performed, and psychological assessment was not practicable. The patient was given amitriptyline (up to 150 mg/d) and cyamepromazine (60 mg/d) for 10 days with no improvement. He was then transferred to our department.

The amitriptyline therapy was discontinued because of a long QT interval on an electrocardiogram. The diagnosis "severe depressive episode with psychotic symptoms" was assigned according to the ICD 10 criteria. Because we initially failed to recognize the association between the mefloquine and the depression, the patient received his third and final dose of mefloquine 2 days after admission to our ward (cumulative dose 1750 mg). He received 6 sessions of right unilateral electroconvulsive therapy with brief pulse stimulus over 11 days. He became manic after the sixth session. He was discharged a week later, hypomanic with chlorpromazine (75 mg/d).

Three weeks after discharge, the man was euthymic, the chlorpromazine therapy was discontinued and treatment with carbamazepine was started. The carbamazepine was continued for 3 years with good compliance, as assessed by biannual measurement of blood levels. He was followed up yearly for another 3 years without psychotropic medication. During this 6-year follow-up, he received verapamil (120 mg/d) for cardiologic purposes, had no relapse and continued to manage his chartered accountant agency successfully.

The patient had no personal or family psychiatric history. He had received no medication other than mefloquine and had not used any recreational drugs. The only stressful life event that could be identified was a tax inspection that occurred a few months before the episode. There was no social or cultural precipitant during his trip to the Far East.

Mefloquine is an antimalarial agent known to have depressogenic properties. The prevalence of depression among people taking mefloquine has been estimated to be as high as 1.2%.[1] However, the incidence of serious psychiatric side effects is considered to be extremely low[2] and, as in our case, such side effects occur most often before the third dose.[3] According to a MEDLINE database search, our case is the first mefloquine-induced bipolar disorder in a patient without a psychiatric history and the first case of psychotic depression without hallucinations or confusion. To the best of our knowledge, it is also the first report of mefloquine-induced depression with a follow-up longer than just a few months. Our patient's mefloquine plasma levels were unfortunately not assayed, but psychiatric reactions to mefloquine are probably not related to an excessive plasma concentration.[2] Although verapamil has not clearly demonstrated mood-stabilizing qualities,[4] we cannot rule out that this drug played a role in preventing relapse. The good outcome may merely be the natural course of the man's bipolar illness. But the late onset of a bipolar disorder, the absence of a personal or family history of mood disorders, the close chronological drug–event relationship and the absence of relapse after 6 years' follow-up (including 3 years without psychotropic medication) support the causative role of mefloquine. Moreover, this case indicates that a psychotic depression can be attributed to mefloquine even when visual hallucinations or confusion, symptoms usually associated with a toxic or neurological cause and not a psychiatric one, are absent. This case also indicates that mefloquine-induced depression may switch to mania when treated with electroconvulsive therapy.

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Clozapine and sialorrhea: update

Among the frequently reported side effects of clozapine is nocturnal hypersalivation (sialorrhea), a troubling and potentially hazardous reaction. Hypersalivation can also occur in the daytime, causing social withdrawal and isolation because of embarrassment and stigma.

Many interventions have been used to alleviate this side effect, including dose reduction, addition of antiparkinsonian agents such as benztropine and procyclidine, and use of sugarless candy. For the most part, these interventions work at the systemic level and have not provided any real relief.

As reported in the May 1999 issue of the *Journal of Psychiatry & Neuroscience*, atropine eye drops were tried as a possible intervention.[1] One drop of 1% solution was given sublingually at bedtime, and the dose was titrated as required to achieve maximum relief of symptoms. We reported encouraging results from this intervention.

The use of atropine eye drops to treat clozapine-induced sialorrhea appears to have a beneficial effect despite the presence of an anticholinergic action. However, patients reported that the atropine was short acting and that they experienced rebound sialorrhea in the early hours of the morning, which necessitated repeat dosing. Some patients reported difficulty manipulating the dropper to ensure the proper dosing. The potential for accidental overdose with drops as opposed to a metered spray was worrisome as well. We therefore have looked for other alternatives to atropine eye drops.

Ipratropium bromide (Atrovent) nasal spray is a powerful, longer acting anticholinergic drug that can also be applied sublingually. The spray formulation comes in 2 concentrations: 0.03% and 0.06%. We have been working with the 0.03% solution, normally used to relieve side effects of severe rhinitis, and have found that 2 sprays of this solution under the tongue at bedtime is as effective, if not more effective, than the 1% atropine eye drops in controlling sialorrhea.

Ten patients, formerly receiving atropine eye drops, were successfully switched to ipratropium bromide nasal spray, 0.03% solution, over 6 months. In 2 cases, use of the nasal spray was started directly. Patients reported reduction or resolution of nocturnal hypersalivation after using the spray. Two patients used the preparation twice a day, the remainder only once a day. There were no side effects other than 2 patients reporting that they did not like the taste. Compared with the eye drops, the metered spray was reported to be easier to use and to require less digital precision. In addition, patients were more accepting of carrying the spray with them and using it in public places.

Although further study is required, we find these observations encouraging in the treatment of clozapine-induced sialorrhea. A protocol for studying the effectiveness of this intervention is currently being submitted to an ethics review board for approval.

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A short form of the Wisconsin Card Sorting Test

There has been a proliferation of studies of cognitive changes with antipsychotic medications since clozapine was reintroduced to clinical practice 10 years ago, and recent reviews have indicated the extraordinary value of cognitive improvement to sociovocational rehabilitation.[1-3] However, the cognitive test batteries remain too long and complicated for general clinical application, discouraging to both clinicians and patients. In our clinic, we are identifying a series of relatively simple but standardized psychometric tests capable of detecting changes from treatment. In this pursuit, we have examined a short form of the Wisconsin Card Sorting Test (WCST)[4] and have found promising results.

Myriad cognitive impairments are associated with schizophrenia, but most would agree that executive function deficits are a leading barrier to vocational reintegration.